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## STEREOCHEMISTRY OF VINYLOGOUS RUBOTTOM OXIDATION OF PROLINE-FUSED CYCLOHEXADIENOL SILYL ETHER<sup>†</sup>

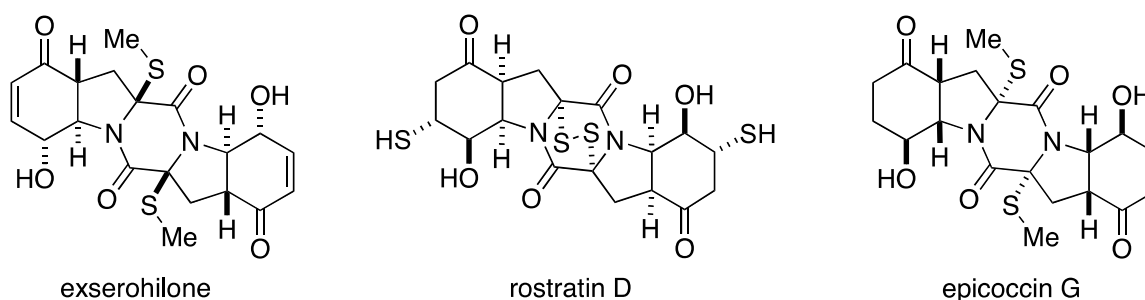
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**Abstract** – The steric effect of vinylogous Rubottom oxidation of proline-fused cyclohexadienol silyl ether was investigated. The facial selectivity in the oxidation is governed by a synergistic effect of the proximal ester and a protective group on the nitrogen.

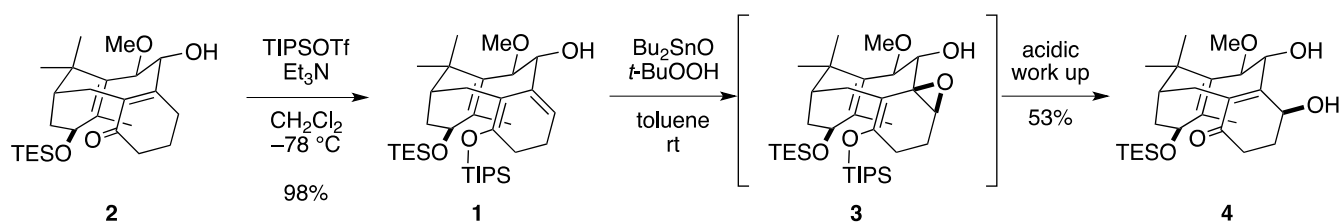
$\gamma$ -Hydroxyenone and its derivatives are often found in a variety of biologically active natural products<sup>1</sup> (Figure 1). Representatively,  $\gamma$ -hydroxyenone is synthesized via Diels–Alder cycloaddition of singlet oxygen and a 1,3-diene followed by basic treatment (Kornblum–DeLaMare rearrangement),<sup>2</sup> desymmetrization of a 1,4-diol,<sup>3</sup> or ring opening of a  $\beta,\gamma$ -epoxycyclohexanone with a base<sup>4a</sup> or acid.<sup>4b</sup> As a direct method from an enone, stepwise transformation such as radicalic bromination followed by silver-mediated hydration has been employed by Allen and Danishefsky<sup>5</sup> because allylic oxidation of an enone is generally difficult under  $\text{SeO}_2$ - or  $\text{CrO}_3$ -mediated conditions as a consequence of its electron-poor nature.<sup>6</sup>



**Figure 1.** Natural products with a proline-fused  $\gamma$ -hydroxy-cyclohexenone/cyclohexanone framework

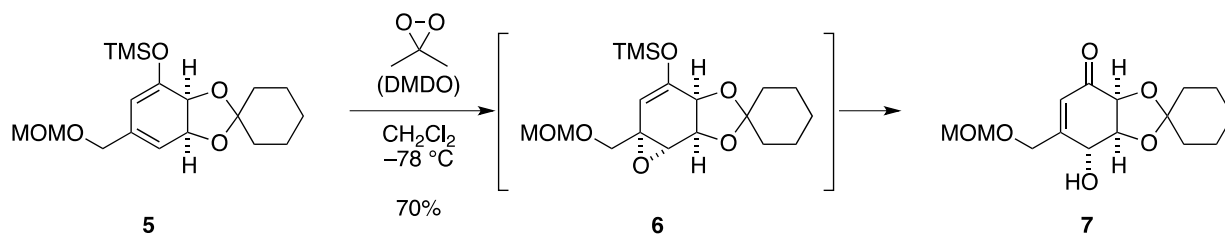
<sup>†</sup>This paper is dedicated to Professor Dr. Isao Kuwajima on the occasion of his 77<sup>th</sup> birthday.

As an alternative method starting from a cyclohexanone derivative, Kuwajima and co-workers reported a vinylogous Rubottom oxidation of siloxydiene **1** (Scheme 1).<sup>7</sup> Because of the steric bias of the bicyclic system, enone **2** was exclusively converted into siloxydiene **1**. Regio- and face-selective epoxidation and acidic ring opening of the resultant epoxide **3** provided  $\gamma$ -hydroxyenone **4** in 53% yield.



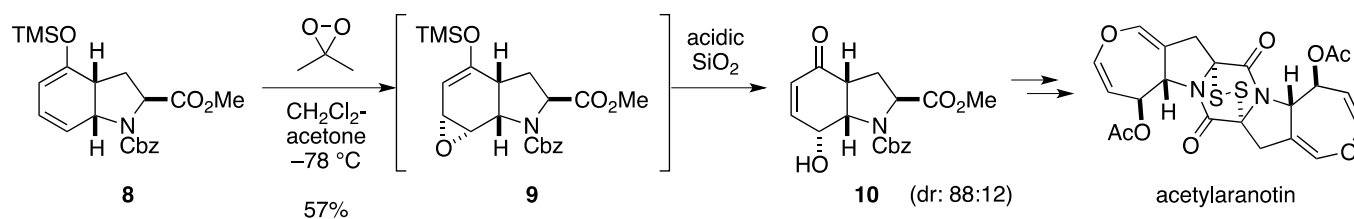
**Scheme 1.** Kuwajima's vinylogous Rubottom oxidation

Grierson also reported a similar vinylogous Rubottom oxidation (Scheme 2).<sup>8</sup> Epoxidation of bicyclic siloxydiene **5** with dimethyldioxirane (DMDO) occurred smoothly, even at  $-78\text{ }^{\circ}\text{C}$ , from the convex face to give **6**, which was transformed into  $\gamma$ -hydroxyenone **7** in 70% yield.



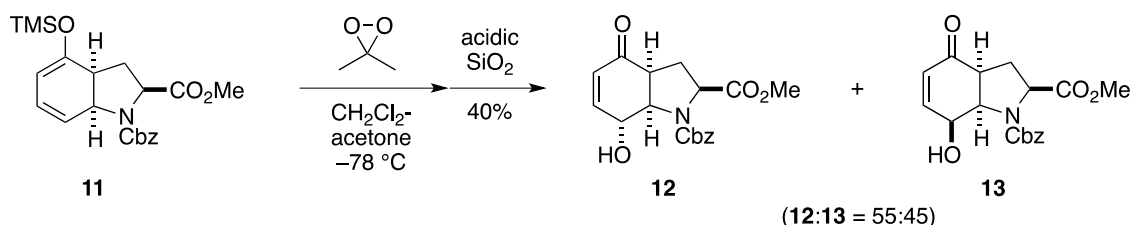
**Scheme 2.** Grierson's vinylogous Rubottom oxidation

During the synthetic studies on acetylaranotin, we had to introduce a hydroxyl group at the  $\gamma$ -position of cyclohexenone (Scheme 3).<sup>9</sup> On the basis of these precedents, we expected that the vinylogous Rubottom oxidation of proline-fused cyclohexadienol silyl ether **8** should occur from the convex face. However, the oxidation proceeded via unexpected  $\alpha$ -epoxide **9** to give  $\gamma$ -hydroxyenone **10** with unnatural stereochemistry;  $\gamma$ -hydroxyenone **10** was subsequently converted into acetylaranotin via inversion of the hydroxyl group at the final stage of the total synthesis. Herein, we investigated the rationale for the unusual face selectivity in the oxidation and clarified that a synergistic effect of the proximal ester and a protective group on the nitrogen plays a key role in this synthesis.



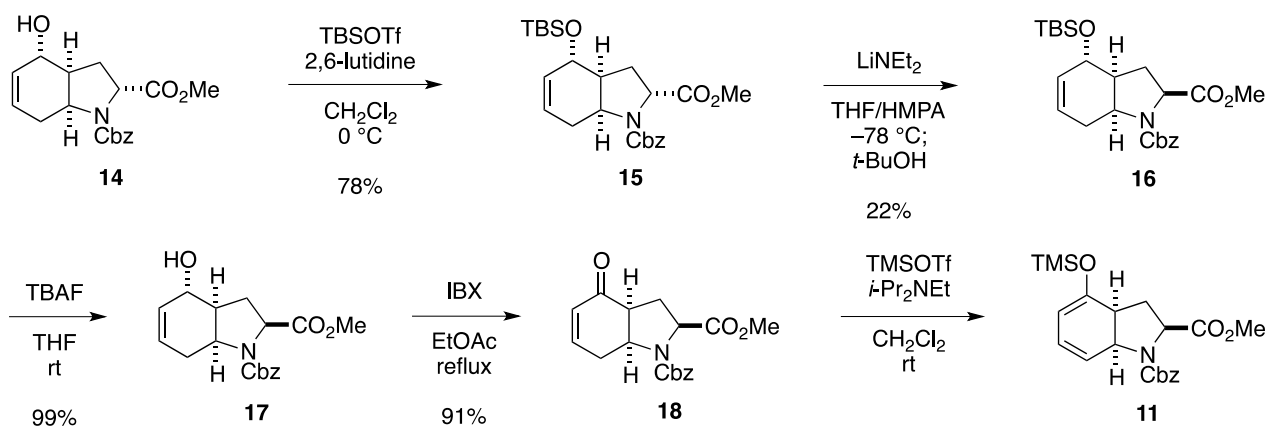
**Scheme 3.** Unexpected face selectivity in the vinylogous Rubottom oxidation

Because we were interested in the unexpected face selectivity in the vinylogous Rubottom oxidation, we first investigated the steric effect of the methyl ester and observed that subjecting diastereomer **11** to the vinylogous Rubottom oxidation provided a mixture of the major isomer **12** and diastereomer **13** in 40% as a combined yield (Scheme 4).<sup>10</sup>



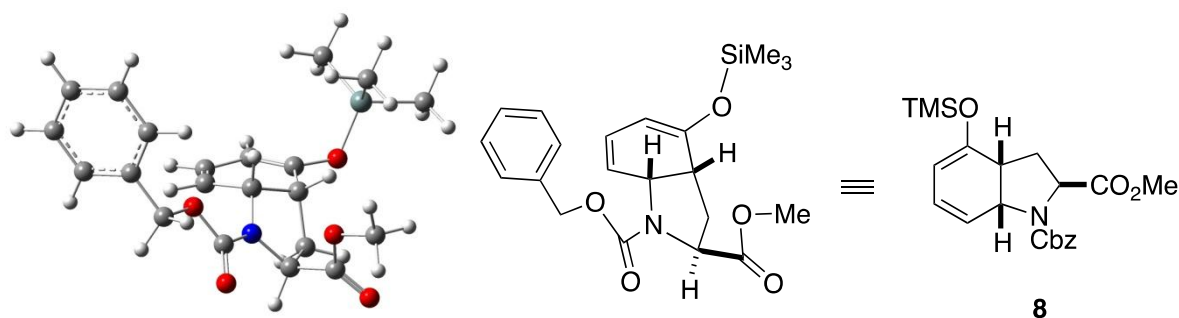
**Scheme 4.** Vinylogous Rubottom oxidation of diastereomer **11**

Diastereomer **11** was prepared via epimerization of the  $\alpha$ -position of the methyl ester (Scheme 5). The synthesis commenced with TBS protection of the allylic alcohol **14**<sup>9</sup> for the subsequent epimerization. Treatment of compound **15** with lithium diethylamide in THF/HMPA followed by kinetic protonation using *t*-BuOH provided the corresponding epimer **16**, albeit in low yield.<sup>11</sup> The allylic TBS ether was then converted into enone **18** in a two-step sequence, and **18** was transformed to dienol silyl ether **11** for the key vinylogous Rubottom oxidation.



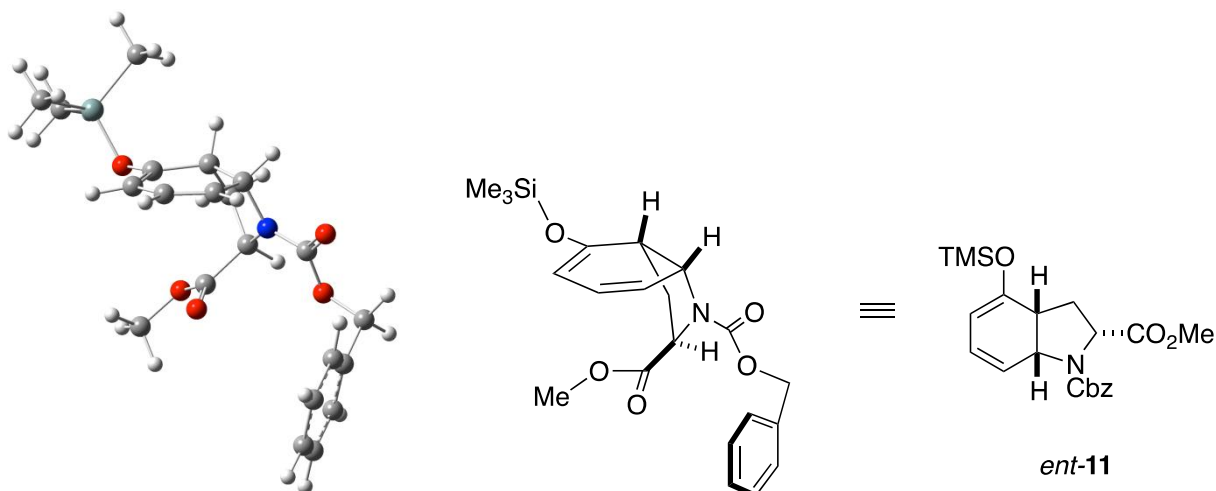
**Scheme 5.** Preparation of proline-fused cyclohexadienol silyl ether **11**

To clarify the reason for the face selectivity that was controlled by the stereochemistry of the ester group, we calculated the most stable conformation of dienol silyl ether **8** using the MMFF94 molecular-mechanics force field in conjunction with the program CONFLEX7<sup>12</sup> (Figure 2). Interestingly, in the most stable conformation of cyclohexadienol silyl ether **8** with a pseudoequatorial methyl ester, in addition to the trimethylsilyl group, the benzyloxy group of the Cbz carbamate locates opposite the methyl ester (*s-trans* conformation to the methane carbon bearing the ester moiety) to reduce steric repulsion. Therefore, the aromatic ring sterically shielded the upper  $\pi$ -face (convex face) of diene **8**, resulting in preferential oxidation at the concave face.



**Figure 2.** Most stable conformation of cyclohexadienol silyl ether **8**

In contrast, in the most stable conformation of dienol silyl ether *ent*-**11**, whose stereochemistry at the ester  $\alpha$ -position is opposite that of compound **8**, the ester group locates at the pseudoaxial position (Figure 3). In addition, the pseudoequatorial  $\alpha$ -proton of the ester forces the benzyloxy group of the Cbz group to adopt the *s-cis* conformation to the methane carbon bearing the ester moiety. The trimethylsilyl group shields the upper  $\pi$ -face (convex face), which should result in the decrease of face selectivity and lower yield of the corresponding products.



**Figure 3.** Most stable conformation of dienol silyl ether *ent*-**11**

In conclusion, the unexpected facial selectivity in the vinylogous Rubottom oxidation was controlled by the stereochemistry of the proximal methyl ester. These results indicate that switching of the stereochemistry of the ester leads to a  $\gamma$ -hydroxyenone with another relative stereochemistry, which provides a guide to the stereochemistry of the ester for the synthesis of proline-fused  $\gamma$ -hydroxycyclohexenone and structurally related natural products, such as exserohilone, rostratins, and epicoccins.

## EXPERIMENTAL

**General Remarks:** Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Anhydrous THF and dichloromethane were purchased from Kanto Chemical Co. Inc. Anhydrous diisopropylethylamine was dried and distilled according to the standard protocols. DMDO was prepared according to the reported procedure and titrated prior to use.<sup>13</sup> Flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40–50  $\mu$ m) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F<sub>254</sub> glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on a JASCO FT/IR-4100 spectrometer. NMR spectra were recorded on a JEOL ECA600 spectrometer and JNM-AL400 spectrometer. For <sup>1</sup>H NMR spectra, chemical shifts are expressed in parts per million downfield from internal tetramethylsilane ( $\delta$  0) or relative internal CHCl<sub>3</sub> ( $\delta$  7.26). For <sup>13</sup>C NMR spectra, chemical shifts are expressed in ppm downfield from relative internal CDCl<sub>3</sub> ( $\delta$  77.0). Mass spectra were recorded on a Bruker micrOTOF II (ESI).

**(2*R*,3*aS*,4*S*,7*aS*)-(+)-1-Benzyl 2-methyl 4-hydroxy-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-indole-1,2-dicarboxylate (14):** a colorless oil. The analytical data (*R<sub>f</sub>*, IR, HRMS, <sup>1</sup>H and <sup>13</sup>C NMR) were identical with those reported in the literature.<sup>9</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> 118 (*c* 1.03, CHCl<sub>3</sub>).

**Formation of dienol silyl ether and vinylogous Rubottom Oxidation.** A flame-dried 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with enone **18** (22.5 mg, 68.3  $\mu$ mol), *i*-Pr<sub>2</sub>NEt (35.0  $\mu$ L, 205  $\mu$ mol), and dry CH<sub>2</sub>Cl<sub>2</sub> (0.68 mL) under an argon atmosphere. To the solution was added TMSOTf (24.7  $\mu$ L, 137  $\mu$ mol) and the mixture was stirred at room temperature. To the resulting mixture was added additional TMSOTf after 30 min (2.5  $\mu$ L, 14  $\mu$ mol) and 40 min (2.5  $\mu$ L, 14  $\mu$ mol), respectively. The resulting mixture was stirred for another 10 min, after which time TLC (hexanes-EtOAc = 6:1, developed twice) indicated complete consumption of **18**. The reaction mixture was cooled to 0 °C and was treated with 1 M aqueous HCl. The organic layer was separated and washed with H<sub>2</sub>O three times and brine. The organic extracts were dried over anhydrous

sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude dienol silyl ether **11**.

The crude dienol silyl ether **11** was diluted with dry CH<sub>2</sub>Cl<sub>2</sub> (0.91 mL), and the mixture was treated with DMDO (0.104 M in acetone, 660 μL, 68.6 μmol) at -78 °C. The resulting suspension was stirred at -78 °C for 30 min, after which time TLC (hexanes-EtOAc = 1:1) indicated complete consumption of **11**. The organic solvents were removed under reduced pressure to give a crude material, which was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and treated with acidic silica gel (1 g). The resulting mixture was dried under reduced pressure and passed through glass filter using EtOAc as an eluent. The filtrate was concentrated under reduced pressure give a crude γ-hydroxyenone, which was purified by preparative TLC (CH<sub>2</sub>Cl<sub>2</sub>-MeOH = 40:1, developed five times) to afford γ-hydroxyenone **12** (5.2 mg, 15 μmol, 22%) and **13** (4.0 mg, 12 μmol, 18%).

**(2*S*,3*aS*,7*R*,7*aR*)-(+)-1-Benzyl 2-methyl 7-hydroxy-4-oxo-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-indole-1,2-dicarboxylate (**12**):** colorless oil:  $R_f = 0.61$  (CH<sub>2</sub>Cl<sub>2</sub>-MeOH = 40:1, developed three times); IR (neat, cm<sup>-1</sup>): 3428, 3033, 2953, 1747, 1678, 1419, 1354, 1306, 1244, 1217, 1120, 1073, 793, 749, 699; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.49–7.28 (m, 5H), 6.88 (dd, 1H,  $J = 10.4, 2.0$  Hz), 6.03 (dd, 1H,  $J = 10.4, 2.0$  Hz), 5.24 (d, 1H,  $J = 12.0$  Hz), 5.07 (d, 1H,  $J = 12.0$  Hz), 4.88–4.78 (m, 2H), 4.49–4.36 (m, 2H), 3.79 (s, 0.5H), 3.54 (s, 2.5H), 3.07 (ddd, 1H,  $J = 13.2, 8.4, 8.4$  Hz), 2.67 (ddd, 1H,  $J = 13.2, 7.6, 7.6$  Hz), 1.97 (ddd, 1H,  $J = 12.8, 12.8, 9.6$  Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 195.3, 172.1, 156.4, 150.5, 135.3, 128.6, 128.5, 128.3, 127.1, 70.1, 68.4, 65.5, 59.3, 52.5, 45.7, 32.9;  $[\alpha]_D^{25} 20.8$  (c 0.380 CHCl<sub>3</sub>); HRMS (ESI): Calcd. for Calcd. for C<sub>18</sub>H<sub>19</sub>NNaO<sub>6</sub> (M<sup>+</sup>+Na), 368.1105; Found: 368.1104.

**(2*S*,3*aS*,7*S*,7*aR*)-(+)-1-Benzyl 2-methyl 7-hydroxy-4-oxo-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-indole-1,2-dicarboxylate (**13**):** colorless oil:  $R_f = 0.55$  (CH<sub>2</sub>Cl<sub>2</sub>-MeOH = 40:1, developed three times); IR (neat, cm<sup>-1</sup>): 3461, 2953, 1748, 1707, 1683, 1418, 1358, 1299, 1212, 1125, 1095, 1016, 769, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.47–7.27 (m, 5H), 6.99–6.86 (m, 1H), 6.20–6.10 (m, 1H), 5.21 (d, 0.5H,  $J = 12.4$  Hz), 5.18–5.07 (m, 1H), 5.03 (d, 0.5H,  $J = 12.4$  Hz), 4.62 (ddd, 1H,  $J = 18.8, 10.4, 8.0$  Hz), 4.46 (dd, 0.5H,  $J = 6.8, 6.8$  Hz), 4.37 (dd, 0.5 H,  $J = 8.0, 8.0$  Hz), 3.79 (s, 1.5H), 3.56 (s, 1.5H), 3.35–3.22 (m, 0.5H), 3.17–3.04 (m, 0.5H), 2.84–2.69 (m, 1H), 2.37–2.16 (m, 2H); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, 100 °C): δ 7.39–7.26 (m, 5H), 6.92 (ddd, 1H,  $J = 10.4, 5.6, 2.4$  Hz), 5.99 (dd, 1H,  $J = 10.4, 2.4$  Hz), 5.51 (s, 1H), 5.14–5.02 (m, 2H), 4.41 (dd, 1H,  $J = 9.2, 7.6$  Hz), 4.21 (dd, 1H,  $J = 8.4, 7.6$  Hz), 3.61 (s, 3H), 2.32–2.25 (m, 1H), 2.11 (dd, 1H,  $J = 13.2, 10.0$  Hz) (two protons are missing due to overlap); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 197.6, 197.4, 173.1, 173.0, 154.2, 153.9, 149.3, 149.0, 136.1, 136.0, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 125.6, 79.8, 79.2, 67.5, 67.4, 63.6, 63.3, 58.3, 58.1, 52.7, 52.4, 41.3, 40.3, 32.0. 31.6

(complexity due to rotamers);  $[\alpha]_D^{27}$  35.9 (*c* 0.320 CHCl<sub>3</sub>); HRMS (ESI): Calcd. for C<sub>18</sub>H<sub>19</sub>NNaO<sub>6</sub> (M<sup>+</sup>+Na), 368.1105; Found: 368.1086.

**(2R,3aS,4S,7aS)-(+)-1-Benzyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (15):** A flame-dried 50-mL two-necked round-bottomed flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and an inlet adapter with three-way stopcock was charged with allyl alcohol **14** (447 mg, 1.35 mmol), 2,6-lutidine (314  $\mu$ L, 2.70 mmol) and dry CH<sub>2</sub>Cl<sub>2</sub> (13.5 mL) under argon atmosphere. To the solution was added TBSOTf (371  $\mu$ L, 1.62 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, after which time TLC (hexanes-EtOAc = 1:1) indicated complete consumption of **14**. The reaction was quenched with 1 M aqueous HCl, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (hexanes-EtOAc = 6:1) to afford TBS ether **15** (469 mg, 1.05 mmol, 78%) as a colorless oil.  $R_f$  = 0.66 (hexanes-EtOAc = 1:1); IR (neat, cm<sup>-1</sup>): 3033, 2953, 1750, 1710, 1413, 1351, 1294, 1204, 1176, 1119, 1067, 1042, 874, 837, 775, 749, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.40–7.25 (m, 5H), 5.77–5.57 (m, 2H), 5.26–5.18 (m, 1H), 5.10 (d, 0.5H, *J* = 12.8 Hz), 4.99 (d, 0.5H, *J* = 12.0 Hz), 4.36–4.26 (m, 1H), 4.21–4.10 (m, 1H), 4.05–3.93 (m, 1H), 3.76 (s, 1.5H), 3.55 (s, 1.5H), 2.85–2.74 (m, 0.5H), 2.67–2.42 (m, 1.5H), 2.10–1.83 (m, 2H), 1.81–1.63 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  172.9, 172.6, 154.7, 154.1, 136.4, 136.3, 129.5, 128.5, 128.3, 128.2, 127.80, 127.77, 127.7, 127.65, 127.6, 125.6, 125.1, 67.6, 67.0, 66.9, 66.7, 58.0, 57.8, 52.7, 52.1, 51.9, 51.5, 44.0, 43.4, 32.8, 31.6, 27.9, 27.4, 25.69, 25.66, 18.0, 17.9, –4.6, –4.7, –4.8 (complexity due to rotamers);  $[\alpha]_D^{25}$  97.6 (*c* 1.62, CHCl<sub>3</sub>); HRMS (ESI): Calcd. for C<sub>24</sub>H<sub>36</sub>NO<sub>5</sub>Si (M<sup>+</sup>+H), 446.2357; Found: 446.2346.

**(2S,3aS,4S,7aS)-(+)-1-Benzyl 2-methyl 4-((*tert*-butyldimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1H-indole-1,2-dicarboxylate (16):** A flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an inlet adapter with three-way stopcock was charged with diethylamine (400  $\mu$ L, 3.87 mmol) and dry THF (10 mL) under argon atmosphere. To the solution was added *n*-BuLi in hexane (1.52 M, 2.34 mL, 3.56 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min. A portion of this solution (5.5 mL) was discarded via syringe, and the rest of the resulting solution was then cooled to –78 °C. Another flame-dried 50-mL two-necked round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and an inlet adapter with three-way stopcock was charged with TBS ether **15** (224 mg, 503  $\mu$ mol) and dry THF (14.4 mL) under an argon atmosphere. While the previously described solution was stirred for 20 min at –78 °C, HMPA (1.44 mL) and the

solution of substrate **15** in THF were added. The resulting mixture was stirred for 20 min before quenching with *t*-BuOH (1.41 mL) in dry THF (2.83 mL), followed immediately by saturated aqueous NH<sub>4</sub>Cl at -78 °C and the aqueous layer was extracted twice with Et<sub>2</sub>O. The combined organic layers were washed with 1 M aqueous HCl and saturated aqueous NaHCO<sub>3</sub>. The organic extracts were dried over anhydrous sodium sulfate, and filtered. The organic solvents were removed under reduced pressure to give a crude TBS ether **16**, which was purified by MPLC (toluene-Et<sub>2</sub>O = 19:1) and GPC to afford TBS ether **16** (48.6 mg, 109 μmol, 22%) as a colorless oil. *R<sub>f</sub>* = 0.65 (hexanes-EtOAc = 1:1); IR (neat, cm<sup>-1</sup>): 3032, 2953, 1751, 1709, 1415, 1352, 1292, 1200, 1175, 1110, 1071, 1042, 871, 837, 774, 745, 697; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.40–7.27 (m, 5H), 5.78–5.57 (m, 2H), 5.24–4.94 (m, 2H), 4.42–4.09 (m, 2H), 4.07–3.98 (m, 1H), 3.75 (s, 1.5H), 3.56 (s, 1.5H), 2.86–2.72 (m, 0.5H), 2.71–2.58 (m, 0.5H), 2.44–2.28 (m, 2H), 2.26–2.11 (m, 1H), 1.81–1.64 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 173.3, 173.1, 154.6, 154.0, 136.5, 128.4, 127.9, 127.8, 125.8, 125.6, 67.1, 66.7, 58.5, 52.4, 52.2, 52.0, 51.8, 45.8, 45.2, 32.8, 31.9, 27.4, 27.0, 25.8, 18.1, -4.5, -4.8 (complexity due to rotamers); IR (neat, cm<sup>-1</sup>): 3032, 2953, 1751, 1709, 1415, 1352, 1042, 837, 774; [α]<sub>D</sub><sup>24</sup> 50.5 (*c* 0.700, CHCl<sub>3</sub>); HRMS (ESI): Calcd. for C<sub>24</sub>H<sub>36</sub>NO<sub>5</sub>Si (M<sup>+</sup>+H), 446.2357; Found: 446.2359.

**(2*S*,3*aS*,4*S*,7*aS*)-(+)-1-Benzyl 2-methyl 4-hydroxy-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-indole-1,2-dicarboxylate (**17**):** A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with TBS ether **16** (46.4 mg, 104 μmol) and dry THF (208 μL). To the solution was added TBAF in THF (1 M, 208 μL, 208 μmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h, after which time TLC (hexanes-EtOAc = 6:1, developed twice) indicated incomplete consumption of **16**. To the reaction mixture was added additional TBAF in THF (1 M, 52.0 μL, 52.0 μmol). After another 1.5 h, the reaction mixture was treated with saturated aqueous NH<sub>4</sub>Cl and aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The organic solvents were removed under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (hexanes-EtOAc = 1:1) to afford allyl alcohol **17** (34.2 mg, 103 μmol, 99%) as a colorless oil. *R<sub>f</sub>* = 0.20 (hexanes-EtOAc = 1:1); IR (neat, cm<sup>-1</sup>): 3444, 3031, 2952, 1748, 1697, 1417, 1356, 1294, 1215, 1001, 751, 698; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.45–7.29 (m, 5H), 5.86–5.70 (m, 2H), 5.24–4.97 (m, 2H), 4.44–4.16 (m, 2H), 4.14–4.02 (m, 1H), 3.76 (s, 1.5H), 3.56 (s, 1.5H), 2.87–2.75 (m, 0.5H), 2.72–2.60 (m, 0.5H), 2.52–2.39 (m, 2H), 2.36–2.21 (m, 1H), 1.80–1.65 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 173.2, 173.1, 154.5, 154.2, 136.5, 136.3, 128.5, 128.4, 128.0, 127.8, 127.2, 126.2, 126.0, 67.1, 65.5, 58.5, 58.4, 52.3, 52.1, 51.6, 51.1, 44.7, 44.2, 32.8, 31.8, 27.5, 27.0; IR (neat, cm<sup>-1</sup>): 2924, 2856, 1695, 1452, 1435, 1267, 1258, 1016, 868; [α]<sub>D</sub><sup>24</sup> 42.9 (*c* 0.590, CHCl<sub>3</sub>); HRMS (ESI): Calcd. for C<sub>18</sub>H<sub>21</sub>NNaO<sub>5</sub> (M<sup>+</sup>+Na), 354.1312; Found: 354.1309.

(2*S*,3*aS*,7*aS*)-(+)-1-Benzyl 2-methyl 4-oxo-2,3,3*a*,4,7,7*a*-hexahydro-1*H*-indole-1,2-dicarboxylate (**18**): A 10-mL screw-top test tube equipped with a Teflon-coated magnetic stirring bar was charged with allyl alcohol **17** (34.2 mg, 103  $\mu\text{mol}$ ), IBX (43.4 mg, 155  $\mu\text{mol}$ ) and EtOAc (413  $\mu\text{L}$ ). The resulting mixture was stirred at reflux for 25 min, after which time TLC (hexanes-EtOAc = 1:1) indicated complete consumption of **17**. The reaction mixture was cooled to room temperature and passed through a pad of Celite using EtOAc as an eluent. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by flash silica gel chromatography (hexanes-EtOAc = 2:1 to 1:1) to afford enone **18** (31.0 mg, 94.1  $\mu\text{mol}$ , 91%) as a colorless oil.  $R_f$  = 0.43 (hexanes-EtOAc = 1:1); IR (neat,  $\text{cm}^{-1}$ ): 3033, 2952, 1748, 1707, 1673, 1415, 1355, 1296, 1208, 1175, 1113, 1001, 750, 699;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.49–7.28 (m, 5H), 7.03–6.81 (m, 1H), 6.19–6.02 (m, 1H), 5.27–4.98 (m, 2H), 4.68–4.34 (m, 2H), 3.76 (s, 1.5H), 3.57 (s, 1.5H), 3.23–2.84 (m, 2H), 2.83–2.56 (m, 2H), 2.24–1.99 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  196.7, 172.7, 154.0, 153.8, 147.6, 147.3, 136.0, 128.5, 128.4, 128.2, 128.1, 128.0, 127.84, 127.80, 67.5, 67.3, 59.1, 58.8, 56.7, 56.2, 52.5, 52.3, 47.8, 47.1, 32.3, 31.4, 28.3, 27.6;  $[\alpha]_D^{26}$  56.2 ( $c$  1.27,  $\text{CHCl}_3$ ); HRMS (ESI): Calcd. for  $\text{C}_{18}\text{H}_{19}\text{NNaO}_5$  ( $\text{M}^+\text{Na}$ ), 352.1155; Found: 352.1138.

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